**IN THE SPECIFICATION**:

Please amend paragraph [0015] as follows:

[0015] According to the present invention, there is provided a method of immunotherapy to treat cancer by administering an effective amount of a natural cytokine mixture (NCM) including, but not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-67~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, and combinations thereof. Further, the present invention provides a method of immunotherapy to treat cancer by administering an effective amount of cyclophosphamide (CY) and an effective amount of indomethacin (INDO). Various anti-cancer treatment methods are also provided wherein administration of an effective amount of CY occurs along with an effective amount of a nonsteroidal anti-inflammatory drug (NSAID) including, but not limited to, indomethacin (INDO), Ibuprofen, celecoxib (CELEBREX® ~~Celebrex.RTM.~~), rofecoxib (VIOXX® ~~Vioxx.RTM.~~), CoxII inhibitors, and combinations thereof. More specifically, the present invention provides a method of immunotherapy to treat cancer by administering an effective amount of a CY in combination with an effective amount of INDO and an effective amount of IFN-γ ~~IFN-.delta.~~, IL-2, IL-1, and TNF-.alpha.. Additionally, the present invention provides a method of immunotherapy to treat cancer by administering an effective amount of a CY in combination with an effective amount of INDO and an effective amount of recombinant IL-2, recombinant IFN-γ ~~IFN-.delta.~~, recombinant TNF-α ~~TFN-.alpha.~~, and recombinant IL-1. The present invention further provides a synergistic anti-cancer treatment by administering an effective amount of CY and INDO in combination with an NCM described herein. In addition, the present invention provides an anti-metastatic treatment method by promoting differentiation and maturation of immature dendritic cells in a lymph node; allowing presentation by resulting mature dendritic cells of antigen to T-cells to gain immunization of the T-

cells to the antigen; and preventing development of metastasis. Alternatively, the present invention provides an anti-metastatic method by unblocking immunization at a lymph node; and generating systemic immunity. The present invention also provides a skin test and a method of pre-treatment of dendritic cells (DC) by applying an effective amount of CY and INDO in combination with an NCM described herein. The present invention further provides a method of treating monocyte defects characterized by sinus histiocytosis or a negative NCM skin test by applying an effective amount of CY and INDO in combination with an NCM described herein. Finally, the present invention provides compositions and methods for eliciting an immune response to endogenous or exogenous tumor antigens.

Please amend paragraph [0030] as follows:

[0030] By "adjuvant" it is meant a composition with the ability to enhance the immune response to a particular antigen. To be effective, an adjuvant must be delivered at or near the site of antigen. Such ability is manifested by a significant increase in immune mediated protection. Enhancement of immunity is typically manifested by a significant increase (usually greater than 10 fold) in the titer of antibody raised to the antigen. Enhancement of cellular immunity can be measured by a positive skin test, cytotoxic T-cell assay, ELISPOT assay for IFN-γ ~~delta-IFN~~ or IL-2, or T-cell infiltration into the tumor (as described below).

Please amend paragraph [0034] as follows:

[0034] There are two ways to make new T cells to attempt to correct T lymphocytopenia. One way, as in rIL-2 therapy, expands T cells already in the periphery, i.e., memory T cells (CD45RO) (blood, lymph node and spleen). The other involves processing in the thymus of new T cells from bone marrow--derived

precursors. This happens naturally in children but not in adults. These new cells are called recent "thymic emigres" and have the surface marker of "naive" T cells i.e., CD45RA. NCM therapy (plus Thymosin .alpha.1) results in the production of these new T cells as well as expanding preexisting memory T cells. More specifically, the present invention relates to immunization to provide an immune response to antigens, which is either endogenously or exogenously administered. Such antigens in the past may have been believed to be immunogenic while others used in the present invention may have been thought previously to be non-immunogenic. Any antigen can be used with the present invention. Examples of such antigens are EADPTGHSY (SEQ ID NO: 1) (melanoma) from MAGE-1 protein, EVDPIGHLY (SEQ ID NO: 2) (lung carcinoma) from MAGE-3, ~~EVDPIGHLY (lung carcinoma) from MAGE-3,~~ and many others. (See Bellone, et al, Immunology Today, Vol. 20, No. 10, p 457-462 (1999). The present invention is directed towards affecting antigen processing generally; therefore, any antigen can be used with the present invention. The present invention can extend to all forms of tumor antigens and haptens including peptides and/or carbohydrates. The present invention can extend to areas of applicability as in AIDS virus vaccine in HIV+ patients; other difficult to manage situations; renal transplants, aged individuals, and the like.

Please amend paragraph [0035] as follows:

[0035] The present invention utilizes several general derived method steps for obtaining immunization in subjects where such immunization was previously thought to be impossible. More specifically, the present invention provides a method for overcoming immune depression by inducing production of naive T cells. The term "naive" T cells, is meant to mean newly produced T cells, even in adults, wherein these T cells have not yet been exposed to antigen. Such T cells at this stage are non-specific yet capable of becoming specific upon presentation by a mature

dendritic cell having antigen, such as tumor peptides, exposed thereon. Thus, the present invention replenishes or generates new T cells. This is generally accomplished by administering a natural cytokine mixture (NCM). The NCM includes, but is not limited to, IL1, IL2, IL6, IL8, IL10, IL12, IFN-γ ~~.delta.IFN~~, TNF.alpha., G- and GM-CSF, recombinants thereof, and combinations thereof. The amount and proportions of these constituents are detailed below. Preferably, about 150-600 units of IL2 are contained in the NCM.

Please amend paragraph [0037] as follows:

[0037] It is preferable to block endogenous suppression of T cells, such as caused by various cancer lesions. Blocking is effected by the co-delivery of low dose cyclophosphamide (CY) and a non-steroidal anti-inflammatory drug (NSAID). The NSAID of choice is indomethacin (INDO). While INDO is the most effective NSAID, it is also arguably the most toxic. Celecoxib (CELEBREX®) ~~Celebrex.RTM.~~ and rofecoxib (VIOXX®) ~~Vioxx.RTM.~~, Cox II NSAIDS, are also less effective. Ibuprofen was effective, but the histological responses were characteristic of a TH2 rather than TH1 mediated response, this being less desirable. Side effects of NSAIDS are to be aggressively treated with proton inhibitors and a prostaglandin E analog. Zinc and multi-vitamins are useful agents to help restore T cell immunity. Treatment with contrasuppression and zinc without the NCM is ineffective.

Please amend paragraph [0055] as follows:

[0055] The present invention has numerous embodiments. In one embodiment, the present invention provides a method of immunotherapy to treat cancer by administering an effective amount of an NCM including cytokines including, but not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-

CSF, recombinants thereof, and combinations thereof. The above method further includes administering 75 to 500 units IL-2 equivalence, wherein the administering preferably occurs bilaterally into lymphatics that drain into lymph nodes. Alternatively, the administering can occur unilaterally. The NCM is administered for at least one to ten days and up to about twenty days. In one preferred embodiment, administration occurs bilaterally and for about 10 days. The NCM can be administered prior to surgery or radiotherapy. Alternatively, the NCM can be administered during recurrence of tumors. In addition to the NCM, an effective amount of CY can be administered. Furthermore, an effective amount of an NSAID can be administered wherein the NSAID can be, but is not limited to, INDO, Ibuprofen, celecoxib (CELEBREX® ~~Celebrex.RTM.~~), rofecoxib (VIOXX® ~~Vioxx.RTM.~~), CoxII inhibitors, combinations thereof, and any other similar NSAID known to those of skill in the art.

Please amend paragraph [0056] as follows:

[0056] In another embodiment of the present invention, there is provided a method of immunotherapy to treat cancer by administering an effective amount of CY and an effective amount of INDO. Another embodiment of the present invention provides a synergistic anti-cancer treatment method by administering an effective amount of a CY and an effective amount of a NSAID, wherein the NSAID can be, but is not limited to, INDO, Ibuprofen, celecoxib (CELEBREX® ~~Celebrexe~~), rofecoxib (VIOXX® ~~Vioxx.RTM.~~), CoxII inhibitors, combinations thereof, and the like.

Please amend paragraph [0057] as follows:

[0057] Another embodiment of the present invention provides a method of immunotherapy to treat cancer by administering an effective amount of CY in combination with an effective amount of INDO and an effective amount of IFN-γ ~~IFN-~~

~~.delta.~~, IL-2, IL-1, and TNF-.alpha.. A further embodiment is directed towards a method of immunotherapy to treat cancer by administering an effective amount of CY in combination with an effective amount of INDO and an effective amount of recombinant IL-2, recombinant IFN-γ ~~IFN-.delta.~~, recombinant TFN-.alpha., and recombinant IL-1.

Please amend paragraph [0058] as follows:

[0058] A synergistic anti-cancer treatment is also provided by the present invention, wherein the treatment includes the steps of administering an effective amount of CY and INDO in combination with a NCM. The NCM can include, but is not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, combinations thereof, and any other similar cytokine known to those of skill in the art.

Please amend paragraph [0061] as follows:

[0061] Other embodiments of the present invention provide a method of using a natural cytokine mixture as a diagnostic skin test for predicting treatment outcome by administering an NCM intracutaneously and determining a response to the NCM within 24 hours, wherein a negative skin test indicates unresponsiveness to the NCM and predicts failure of patients to respond to surgery with or without radiotherapy. Another embodiment provides a method of pre-treatment of dendritic cells (DC) by applying an effective amount of CY and INDO in combination with an NCM including cytokines such as, but not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, combinations thereof, and any other similar cytokines known to those of skill in the art.

Please amend paragraph [0062] as follows:

[0062] The present invention provides a method of treating monocyte defects characterized by sinus histiocytosis or a negative NCM skin test by applying an effective amount of CY and INDO in combination with an NCM. The NCM includes, but is not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, combinations thereof, and any other similar cytokines known to those of skill in the art.

Please amend paragraph [0063] as follows:

[0063] Further, the present invention provides various methods of eliciting an immune response to endogenous or exogenous tumor antigens by administering an effective amount of an NCM that includes various cytokines including, but not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, or combinations thereof. Another embodiment of the present invention provides administering the NCM described above and an effective amount of CY to elicit an immune response to endogenous or exogenous tumor antigens. In yet another embodiment of the present invention, the method of eliciting an immune response to endogenous or exogenous tumor antigens occurs by administering an effective amount of an NCM; an effective amount of CY; and an effective amount of INDO, wherein the NCM includes cytokines such as, but not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, and combinations thereof.

Please amend paragraph [0064] as follows:

[0064] The present invention also provides a composition for eliciting an immune response to endogenous or exogenous tumor antigens. The composition includes an effective amount of NCM, wherein the NCM includes cytokines such as, but not limited to, IL-1, IL-2, IL-6, IL-8, IL-12, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., GM-CSF, G-CSF, recombinants thereof, and combinations thereof. In a further embodiment, the composition includes an effective amount of CY. In yet another embodiment, the composition further includes an effective amount of INDO.

Please amend paragraph [0120] as follows:

[0120] INDO is the most potent of NSAIDs acting on both cyclooxygenase I & II, but has greater gastrointestinal toxicity. Newer CoXII inhibitors such as celecoxib(CELEBREX® ~~Celebrex.RTM.)~~ and rofecoxib (VIOXX® ~~Vioxx.RTM.~~) are thought to have less gastrointestinal toxicity. Use of these two agents in place of INDO in a small series of patients gave lesser responses as measured by clinical and pathological criteria and by survival. In the case of VIOXX® ~~Vioxx.RTM.~~, all seven patients had clinical signs of gastritis following a week of therapy. In the cervical cancer patients, Ibuprofen was used as the NSAID and good responses were obtained. Based upon these observations INDO is preferred, but CELEBREX® ~~Celebrex~~ or Ibuprofen can be substituted if INDO is not tolerated. VIOXX® ~~Vioxx.RTM.~~ is not recommended. Omeprazole (PRILOSEC®) ~~Prilosec~~ or other proton pump inhibitors with or without an oral prostaglandin analog is recommended as prophylaxis for gastritis, while histamine H.sub.2 blockers are not considered indicative.

Please amend paragraph [0122] as follows:

[0122] Recently low dose recombinant IL-2 was reported to delay recurrence of metastasis and increase mean survival time in patients with H&N SCC (See, DeStefani, et al., 2002, and Valente, et al, 1990). In the prior art research, no clinical responses were observed and lesser tumor changes (lymphoid infiltration without tumor regression) were observed. Nevertheless, rIL-2 can act with CY & INDO to further induce clinical responses and improve survival. Other natural or recombinant cytokines corresponding to those present in the NCM singly or in combination are also potentially active. For example, cytokines such as IL-1, IFN-γ ~~IFN-.delta.~~, TNF-.alpha., IL-6, IL-8, GM-CSF, G-CSF, IL-12, and combinations thereof can be used in natural or recombinant form.

Please amend paragraph [0125] as follows:

[0125] One of these patients had a tumor considered inoperable and was shown to convert the negative test to positive and allowed a second treatment to clinically reduce the tumor and by pathological criteria and to allow prolonged survival following surgery (>7 years). This pretreatment of skin test negative patients with NCM can increase response rates. NCM plus thymosin .alpha..sub.1 can also be predicted to work (See, United States Published Application No. 20030124136). The negative NCM skin test reflects a monocyte defect and treatment with monocyte-active cytokines in natural or recombinant form would be predicted to be useful singly or in combination thereof. These include, but are not limited to, GM-CSF, G-CSF ~~M-CSF~~, IFN-γ ~~IFN-.delta.~~, IL-1, IL-6, II-8, IL-12 and others.

Please insert the attached sequence listing after paragraph [0236].